Statistical Analyses for a Set of Medical Data

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Abstract

Statistical analyses for a nonorthogonal four row by 17 column design involving four treatments are presented. Analyses of variance, tranformation of data, and confidence interval estimation are presented for several responses. A study of residuals is made resulting in the eliminating of responses from several patients and a re-analysis of the remaining data. A possible misconception in combining statistical analyses for sets of nonorthogonal data is discussed.

Introduction

Multiple measurements were collected on a set of 17 patients. The treatment design involved a mixture of drugs; the experiment design was a nonorthogonal patient (row) by visit (column) design with four different treatments for patients suffering asthma attacks. For the experiment the asthma attacks were induced by use of a mediator which was either histamine or methacholine and several responses were measured both before and after the mediator was administered. Several statistical analyses are presented. An outline of the paper follows:

The Treatment Design

The Experimental Plan or the Experiment Design

Statistical Response Models

A Statistical Analysis of the Data on Concentration for Visits 3 and 5 with Histamine

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A Statistical Analysis of the Data on Concentration for Visits 4 and 6 with Methacholine

A Combined Statistical Analysis of the Data on Concentration for Visits 3, 4, 5, and 6

A Statistical Analysis for the Data on Forced Expiratory Volume (FEV) for Visits 3 and 5

A Statistical Analysis for the Data on Forced Expiratory Volume (FEV) for Visits 4 and 6 – ANOVA tables

A Statistical Analysis for FEV, VC, MMEF, SP, DP, and Pulse Data from Visits 3, 4, 5, and 6

Transformations and Additivity Studies for Concentration Data for Visits 1, 3, and 5

An Artificial Example – A Useful Device and a Possible Misconception in Analysis of Nonorthogonal Data

The Treatment Design

The treatment design consisted of the following four treatments for each of two mediators, histamine and methacholine,

Placebo - denoted by P throughout the following discussion

Scholl's 1000-BR - denoted by S throughout the following discussion

Isoproterenol - denoted by I throughout the following discussion

Combination of Isoproterenol and Scholl's 1000-BR - denoted by $C = S + I$.

One could consider this design to be a 2^3-factorial as follows:

Level of I	Histamine level of S	
	0	1
0		
1		

Level of I	Methacholine level of S	
	0	1
0		
1		

where 0 means the drug was absent and 1 means the drug was present in the treatment.

One further aspect of the treatment design is the fact that the treatments were applied in a sequence over the six visits of each of the 17 patients. Sequence

1, for example, was PPSIPC and was given to patients 801 and 813. There were eight sequences of treatments and these are denoted by s_1, s_2, ..., s_8 in the last column of Table 1. These sequences are useful in assessing carry-over effects of one treatment on the next visit of a patient.

Some sequences do not have any letters in common from visit three through visit six; two such sequences are:

PPSIPC = sequence 1

PPISCP = sequence 6 .

As indicated in Table 2, there are six such pairs of sequences. The ten sequences having three letters different are given in column two of Table 2. Likewise, the twelve pairs of sequences having only two letters in common are given in the last column of Table 2.

Since patients are orthogonal to treatments and to visits, the sum of squares among patients may be partitioned as follows, either for all six visits in Table 1 or only the last four visits:

Source of Variation	Degrees of Freedom	F-test
Among patients	16	
Among sequences	7	)
Within sequences	9	)

An F-test of the among-sequences mean square and the within-sequence mean square may be made as indicated in the above table.

An analysis of the above type was not made because no interest in the sequences was indicated by the experimenter.

Table 1. Experimental plan of drug administration to 17 patients on 6 successive visits.

Patient number	Treatment for Visit Number and Mediator*						Sequence of treatment
	1-H	2-M	3-H	4-M	5-H	6-M	
801	P	P	S	I	P	C	S_1
802	P	P	S	I	C	P	S_2
803	P	P	I	S	P	C	S_3
804	P	P	P	S	I	C	S_4
805	P	P	I	P	S	C	S_5
806	P	P	I	S	C	P	S_6
807	P	P	S	P	I	C	S_7
808	P	P	P	I	S	C	S_8
809	P	P	I	S	P	C	S_3
810	P	P	P	S	I	C	S_4
811	P	P	I	S	C	P	S_6
812	P	P	S	I	C	P	S_2
813	P	P	S	I	P	C	S_1
814	P	P	P	I	S	C	S_8
815	P	P	S	P	I	C	S_7
816	P	P	I	P	S	C	S_5
817	P	P	P	S	I	C	S_4

*Treatments are P = placebo, S = Scholl's 1000-BR, I = Isoproterenol, and C = S + I in combination. The two mediators are histamine (H) and methacholine (M). Patient 817 is number 819 in the experiment.

Table 2. Relationships among sequences of treatments in visits 3 to 6.

Pairs of sequences differing by		
Four letters	Three letters	Two letters
S_1 and S_6	S_1 and S_4	S_1 and S_2
S_2 and S_3	S_1 and S_5	S_1 and S_3
S_2 and S_4	S_2 and S_7	S_1 and S_7
S_2 and S_5	S_2 and S_8	S_1 and S_8
S_6 and S_7	S_3 and S_7	S_2 and S_6
S_6 and S_8	S_3 and S_8	S_3 and S_4
	S_4 and S_5	S_3 and S_5
	S_4 and S_6	S_3 and S_8
	S_5 and S_6	S_4 and S_7
	S_7 and S_8	S_4 and S_8
		S_5 and S_7
		S_6 and S_8

The Experimental Plan or the Experiment Design

The experimental plan (or the experiment design) is given in Table 1. There were two mediators, histamine (H) and methacholine (M). The histamine mediator was given on visits 1, 3, and 5 of the 6 visits of these 17 patients to the laboratory or medical center. Methacholine was given to the patients on visits 2, 4, and 6. Thus, the experiment design indicates that three analyses of the data on each characteristic are desired. Also, the doctor knew the identity of the treatments on visits 1 and 2, but the patient did not. This part was a singly blind study. Since neither the doctor nor the patient knew the identity of the treatment on visits 3, 4, 5, and 6, the study was doubly blind for these visits. The three analyses suggested to us are:

(i) An analysis of the data from visits 3 and 5 for the histamine mediator.

(ii) An analysis of the data from visits 4 and 6 for the methacholine mediator.

(iii) An analysis of the data from all four visits combined.

It was not possible to use an appropriate randomization since treatment C could not be administered until both treatments I and S were tried on the patient. Hence, in no case can C appear anywhere but on visits 5 and 6. It is assumed that this restriction on the randomization does not affect the inferences that can be made from these data. Several data analytic approaches will be used to check for confounding between visits 5 and 6 and the results for treatment C.

Statistical Response Models

For the three analyses suggested in the previous section, we shall assume the following linear model for the observations:

Y_{hij} = the response obtained from the jth visit and ith treatment for patient h

$$= \mu + p_h + t_i + v_j + e_{hij} ,$$

where μ is an effect common to all observations, p_h is an effect due to the hth patient, t_i is the effect of the ith treatment, v_j is an effect due to the jth visit, e_{hij} is an error component due to patient h, treatment i, and visit j, the e_{hij} are considered to have mean zero and variance σ_e^2 and to be normally and independently distributed. For the patients of this experiment the expected value of Y_{hij} is $\mu + p_h + t_i + v_j$. If the patients represent a random sample of patients from some specified population of patients, then the expected value of Y_{hij} is $\mu + t_i + v_j$ and the p_h are considered to be independently and identically distributed with mean zero and variance σ_p^2 . Also, $h = 1, 2, \cdots, 17$; $t_i = P, S, I, C$; and $j = 1, 2, 3, 4, 5, 6$.

Another response equation could be

$$Y_{fghi} = \mu + p_h + t_i + m_g + w_{fg} + tm_{ig} + e_{fghi} ,$$

where m_g, g = H or M, is an effect due to the gth mediator, w_{fg} is an effect due to the fth visit using mediator g, and tm_{ig} is an interaction effect of the ith treatment in combination with the gth mediator, and the remaining effects are as described above. One could also add interaction terms for treatments and patients and for patients and visits.

One could also add a one-period residual effect for the ith treatment. It is not believed that a treatment could have an effect beyond the visit on which it is administered. Since not all interaction and/or residual effects can be estimated, one must be cautious about adding additional terms to the model. Perhaps an individual degree of freedom Tukey-type of interaction could be introduced into the model for patient by treatment and patient by mediator types of interaction. Whether or

not this type of model will be sufficient to account for the interactions will need to be investigated.

Also, one group of patients may follow one model and a different group may follow a different model. Some of these possibilities will be investigated.

A Statistical Analysis of the Data on Concentration for Visits 3 and 5 with Histamine

The data for concentration, at which the mediator was stopped, are presented in Table 3 for visits 1, 3, and 5 using the histamine mediator. The data from visit 1 is considered to be the baseline value for a patient. The subtraction of this value from the data from visits 3 and 5 is considered to be a baseline correction. It should be noted that the subtraction of the baseline value does NOTHING but change the size of estimated patient effects and sums of squares involving patient effects. The estimated treatment and visit effects using the first statistical model in the preceding section are identical whether the baseline values are subtracted or not. Hence, it is recommended that these additional computations be omitted. It should also be noted that the subtraction of the baseline value is a covariance analysis using one as the value of the regression coefficient. The above statements hold for any value of the regression coefficient. Computations are carried out, however, (see Tables 4a and 5) to demonstrate this point.

Since the experiment design is highly nonorthogonal, it was necessary to set up the $24 = 1 + 17 + 2 + 4$ normal equations for the mean, 17 patients, 2 visits, and 4 treatments and to solve this set of equations for solutions of parameters. The solutions for the treatment and visit effects are given at the bottom of Table 4, using the statistical model in the first part of the preceding section.

Table 3. Concentration at which the histamine mediator was stopped.

Patient Number	Visits 1	3	5	Total	3 + 5	Visits 3 - 1	5 - 1	Total
801	0.25	0.50	5.00*	5.75	5.50	0.25	4.75*	5.00
802	2.50	5.00	10.00	17.50	15.00	2.50	7.50	10.00
803	0.06	0.06	1.00	1.12	1.06	0.00	0.94	0.94
804	2.50	2.50	1.00	6.00	3.50	0.00	-1.50	-1.50
805	0.25	0.25	0.50	1.00	0.75	0.00	0.25	0.25
806	0.25	0.12	10.00	10.37	10.12	-0.13	9.75	9.62
807	0.06	1.00	0.25	1.31	1.25	0.94	0.19	1.13
808	0.12	0.50	1.00	1.62	1.50	0.38	0.88	1.26
809	0.50	0.25	1.00	1.75	1.25	-0.25	0.50	0.25
810	2.50	10.00*	5.00	17.50	15.00	7.50*	2.50	10.00
811	0.50	0.50	5.00	6.00	5.50	0.00	4.50	4.50
812	0.12	0.25	0.50	0.87	0.75	0.13	0.38	0.51
813	0.06	0.12	0.12	0.30	0.24	0.06	0.06	0.12
814	0.50	5.00*	1.00	6.50	6.00	4.50*	0.50	5.00
815	0.06	2.50	0.25	2.81	2.75	2.44	0.19	2.63
816	0.50	2.50	2.50	5.50	5.00	2.00	2.00	4.00
817	0.12	0.06	0.06	0.24	0.12	-0.06	-0.06	-0.12
Total	10.85	31.11	44.18	86.14	75.29	20.26	33.33	53.59

Total for visits 3 and 5 (number)
P = 25.18(9), I = 10.24(11),
C = 25.50(4), S = 14.37(10)

Totals
P = 18.57(9), I = 2.94(11)
C = 22.13(4), S = 9.95(10)

* Large differences with same treatment P .

Table 4. Analysis of variance, treatment and visit effects and treatment covariance matrix for visits 3 and 5, for concentration data.

Source of variation	Degrees of freedom	Sum of squares	Mean square	F-ratio	$F_{.01}$
Total	34	457.6165			
Correction for mean	1	166.7231			
Patients (ignoring treatments)	16	183.9882	11.4993		
Among sequences	7				
Within sequences	9				
Visits (ignoring treatments)	1	5.0243	5.0243		
Patients x visits (ignoring treatments)	16	101.8809	6.3676		
Treatments (eliminating patients and visits)	3	61.8366	20.6122	6.69	5.74
Remainder	13	40.0443	3.0803		
Visits (eliminating treatments)	1	0.96329			

Treatment effects

$\hat{I} = -2.21$
$\hat{S} = -1.26$
$\hat{P} = -0.03$
$\hat{C} = 3.51$

Visit effects

$\hat{v}_3 = 0.17$
$\hat{v}_5 = -0.17$

Covariance matrix/3.0803

$$\begin{bmatrix} .157407 & .024632 & .046163 & -.063884 \\ 0 & .144737 & .013158 & -.092105 \\ 0 & -.008373 & .168660 & -.180622 \\ 0 & -.003589 & -.070574 & .494019 \end{bmatrix}$$

Table 5. Analysis of variance, treatment and visit effects, and covariance matrices for visit 1 subtracted from 3 and 5.

Source of variation	Degrees of freedom	Sum of squares	Mean square	F-ratio	$F_{.01}$
Total	34	302.9669			
Correction for mean	1	84.4673			
Patients (ignoring treatments)	16	111.5944	6.9746		
Among sequences	7				
Within sequences	9				
Visits (ignoring treatments)	1	5.0243			
Patients x visits (ignoring treatments)	16	101.8809	6.3676		
Treatments (eliminating patients and visits)	3	61.8366	20.6122	6.69	5.74
Remainder	13	40.0443	3.0803		
Visits (eliminating treatments)	1	not computed			

Treatment effects

$\hat{I}$ =

$\hat{S}$ =

$\hat{P}$ =

$\hat{C}$ =

Visit effects

$\hat{v}_3$ =

$\hat{v}_5$ =

} Same as in Table 4

After eliminating the effect of nonorthogonality of visit and patient effects from the treatment effects, we note that there are highly significant differences among treatments, that is F = 6.697, and the tabulated value of F at the one percent point is 5.74. Now looking at the treatment effects, we note that treatment C gives the highest concentration and that treatment I gives the lowest. The variance of this contrast would be

$$[.157407 + .494019 - 0 - (-.063884)]3.0803 = 2.2034 \quad .$$

A t-test would be $t = [3.51 - (-2.21)]/\sqrt{2.203} = 3.85$, which is greater than $t_{.01,13df} = 3.01$. Likewise, the 95% comparisonwise confidence interval is computed as

$$3.51 - (-2.21) \pm 2.160\sqrt{2.2034} = 5.72 \pm 3.206 \quad .$$

Similar values for all possible differences among the four treatment effects are given below.

Differences and 95% comparisonwise confidence intervals for treatment means (or effects) adjusted for visit and patient effects

	Treatment		
Treatment	C	P	S
I	5.72 ± 3.206**	2.18 ± 2.006*	0.95 ± 1.997
S	4.77 ± 3.249**	1.23 ± 2.106	-
P	3.54 ± 3.624 ?	-	-

* Difference significant at 5% level.

** Difference significant at 1% level.

? Difference almost significant at ($t = 2.11$ vs. $t_{.05,13} = 2.16$) at the 5% level.

The significance test used in all cases above was the Student t-test.

The error rate used above was a comparisonwise error rate. Alternatively, one could use a per experiment by using $t_{\alpha/m, df}$, where m = number of comparisons to be made and df = degrees of freedom in the error mean square, instead of $t_{\alpha, df}$ or an experimentwise error rate by using studentized-range values $q_{\alpha, v, df}$, where v = number of treatments, in place of $\sqrt{2}t_{\alpha, df}$. Of course, there are several other error rate bases that could be utilized (e.g., see Chapter II of Experimental Design – Theory and Application, Macmillan Co., N.Y., 1955, by W. T. Federer).

It is surprising that $\hat{P}$, the estimated treatment effect for the P treatment, exceeds the estimated effects, $\hat{I}$ and $\hat{S}$, for the I and S treatments. One might suspect some sort of interaction or one might suspect some unusually large values, outliers, for the P treatment, or some unusually small outliers for the I and S treatments. First, we shall investigate whether or not one might suspect that the error mean square, 3.0803, is unusually large for data of this nature. To do this we look at the data from patients during visits 1 and 2. Now visits 1 and 2 should allow one to estimate what the within- and among-patient variation is for concentration. Before doing this, one should note that the variation in H and in M should be different simply because the range of concentrations for H is zero to 10 while that for M is zero to 25. Therefore, in Table 6 the visit 2 concentrations are multiplied by .4 = 10/25 in an attempt to equalize the variances. The among-patient variance for visit 1 (H) is 0.8169, while that for .4 (visit 2 (M)) is 0.2382 (see Table 6). The patient by visit variance here was 0.2000 (see Table 6). This appeared to overcorrect. Therefore, the uncorrected values for visit 2 were used in the Table 7 calculations. The visit 2 among-patient variance is 1.82 times larger than the visit 1 variance. The patient by visit interaction is 0.3316. None of the variances described here are as large as the residual variance for visits 3 and 5, 3.0803, in Tables 4 and 5. This variance is over 9 times larger than the error variance, 0.3316, that one might consider appropriate. A good share of this large remainder variance

Table 6. Analysis of concentrations on visits 1 and 2 using .4(concentration of visit 2).

Patient number	Visit .1	Visit 2(.4)	Sum	Difference
801	0.25	0.12	0.37	0.13
802	2.50	0.25	2.75	2.25
803	0.06	0.06	0.12	0.00
804	2.50	1.00	3.50	1.50
805	0.25	0.12	0.37	0.13
806	0.25	0.25	0.50	0.00
807	0.06	0.06	0.12	0.00
808	0.12	0.12	0.24	0.00
809	0.50	0.50	1.00	0.00
810	2.50	2.00	4.50	0.50
811	0.50	0.12	0.62	0.38
812	0.12	0.06	0.18	0.06
813	0.06	0.25	0.31	-0.19
814	0.50	0.25	0.75	0.25
815	0.06	0.25	0.31	-0.19
816	0.50	0.12	0.62	0.38
817	0.12	0.06	0.18	0.06
Total	10.85	5.59	16.44	5.26

Sum of squares

Visit 1	19.9951	(17df)
Visit 2 x .4	5.6489	(17df)

Variance among patients

Visit 1	0.8169	(16df)
Visit 2 x .4	0.2382	(16df)

$$\frac{0.8169}{0.2382} = 3.43$$

$$F_{.05}(16,16) = 2.33$$

Source of variation	Degrees of freedom	Sum of squares	Mean square	F-ratio	$F_{.05}$
Total	34	25.6440	-	-	-
Correction for mean	1	7.9492	-	-	-
Patients	16	13.6813	0.8551	4.28	2.33
Visits	1	0.8138	0.8138	4.07	4.49
Patients x visits	16	3.1997	0.2000	-	-
TOTAL - Correction for mean	33	17.6948	0.5362	-	-

Table 7. Analysis of concentrations on visits 1 and 2.

Patient number	Visit 1	Visit 2	Sum	Difference
801	0.25	0.31	0.56	0.06
802	2.50	0.62	3.12	-1.88
803	0.06	0.15	0.21	0.09
804	2.50	2.50	5.00	0.00
805	0.25	0.31	0.56	0.06
806	0.25	0.62	0.87	0.37
807	0.06	0.15	0.21	0.09
808	0.12	0.31	0.43	0.19
809	0.50	1.25	1.75	0.75
810	2.50	5.00	7.50	2.50
811	0.50	0.31	0.81	-0.19
812	0.12	0.15	0.27	0.03
813	0.06	0.62	0.68	0.56
814	0.50	0.62	1.12	0.12
815	0.06	0.62	0.68	0.56
816	0.50	0.31	0.81	-0.19
817	0.12	0.15	0.27	0.03
Total	10.85	14.00	24.85	3.15

Sum of squares

Visit 1 19.9951 (17df)
Visit 2 35.3050 (17df)

Variance among patients

Visit 1 0.8169 (16df)
Visit 2 1.4860 (16df)

$\frac{1.4860}{0.8169} = 1.82$

$F_{.05}(16,16) = 2.33$

Source of variation	Degrees of freedom	Sum of squares	Mean square	F-ratio	$F_{.05}$
Total	34	55.3001	-	-	-
Correction for mean	1	18.1624	-	-	-
Patients	16	31.5082	1.9693	5.94	2.33
Visits	1	0.3233	0.3233	0.97	4.49
Patients x visits	16	5.3062	0.3316	-	-
TOTAL - Correction for mean	33	37.1377	1.1254	-	-

appears to be due to three discrepant values. These are (see asterisk in Table 3):

Patient 810 - visit 3, treatment P

Patient 814, - visit 3, treatment P

Patient 801 - visit 5, treatment P .

Omission of the above three data points and solution of the resulting 24 normal equations results in the following solutions, where $\widehat{\mu + p_h}$ solutions are obtained instead of $\hat{\mu}$ and $\hat{p}_h$:

$\widehat{\mu + p_1} = 1.000$
$\widehat{\mu + p_2} = 5.909$
$\widehat{\mu + p_3} = 2.121$
$\widehat{\mu + p_4} = 3.341$
$\widehat{\mu + p_5} = 1.705$
$\widehat{\mu + p_6} = 4.197$
$\widehat{\mu + p_7} = 1.955$
$\widehat{\mu + p_8} = 1.613$
$\widehat{\mu + p_9} = 2.216$
$\widehat{\mu + p_{10}} = 7.160$
$\widehat{\mu + p_{11}} = 1.887$
$\widehat{\mu + p_{12}} = -1.216$
$\widehat{\mu + p_{13}} = 0.983$
$\widehat{\mu + p_{14}} = 1.706$
$\widehat{\mu + p_{15}} = 2.705$
$\widehat{\mu + p_{16}} = 3.830$
$\widehat{\mu + p_{17}} = 1.651$

Treatment effects

$\hat{P} = -1.124$
$\hat{I} = -2.057$
$\hat{S} = -0.603$
$\hat{C} = 3.784$

Variance-covariance matrix/2.0599

$$\frac{1}{1140}\begin{bmatrix} 380 & 110 & 65 & -112 \\ 0 & 150 & -15 & -132 \\ 0 & 30 & 225 & -72 \\ 0 & 90 & 105 & 696 \end{bmatrix}$$

Visit effects

$\hat{v}_3 = .103$
$\hat{v}_5 = -.103$

From the above solutions for effects, we compute the residuals as:

$$Y_{hij} - \widehat{\mu + p_h} - \hat{t}_i - \hat{v}_j = \hat{e}_{hij} .$$

These are given in Table 8. The largest remaining residuals are now those for patients 806 and 812. The data point for patient 806, visit 5, appears to be too high while that for patient 816, visit 5, appears to be too low. These residuals of the order ±2 are more than three times larger than any of the remaining residuals. An analysis could be, but was not, performed on the data with the above five "discrepant" values removed. One should study characteristics of patients such as these five to determine the sources of their erratic behavior relative to the other patients in this experiment. It is possible that several types of patient response to concentration of a mediator are possible. This may mean that different treatments would be prescribed for different types of asthma sufferers.

An analysis of variance and 95% comparisonwise confidence intervals are presented in Table 9. The remainder mean square from Tables 4 and 5 was 3.0803, while the one in Table 9 is 2.0599. This is a 1/3 reduction but it is still about six times larger than the patient by visit mean square 0.3316 in Table 7. If one were to eliminate the four largest residuals, the resulting mean square would be $[20.5988 - (-2.123)^2 - 2.122^2 - 1.966^2 - (-1.965)^2]/8 = 0.4828$, which is in the same general area as 0.3316 . It appears that using a mean square of 3.0803 is too large for comparing treatment effects as in Tables 4 and 5. It is not clear what should be an appropriate error for visits 3 and 5 data. Note that the data from visits 1 and 2 were singly blind data and hence would probably be expected to be less variable than data from doubly blind tests. Also, any significance statements for the results in Table 4 are probably on the conservative side with respect to Type I errors. Despite this, the only exception in significance statements are that treatment C is now significantly higher than treatment P at the 1% level, whereas it did not reach the 5% level previously, and treatment P is now not significantly higher than treatment I. The estimated treatment effects for both cases are listed below for comparison:

Table 8. Residuals for concentration data with histamine mediator after omitting data for three discrepant values (dashes in the table).

Patient	Visit 3	Visit 5	Sum*
801	0	-	0
802	- .409	+ .410	+.001
803	- .107	+ .106	-.001
804	+ .180	- .181	-.001
805	+ .499	- .499	.000
806	-2.123	2.122	-.001
807	- .455	+ .455	+.000
808	- .092	+ .093	+.001
809	- .012	+ .011	-.001
810	-	0	0
811	+ .567	- .568	-.001
812	1.966	-1.965	+.001
813	- .363	+ .364	+.001
814	-	0	0
815	+ .295	- .295	.000
816	+ .624	- .624	.000
817	- .570	+ .569	-.001
Sum*	.000	- .002	-.002

* Zero within rounding.

Table 9. Analysis of variance for visits 3 and 5 omitting the three discrepant values together with the differences and confidence intervals for estimated treatment effects.

Source of variation	d.f.	Sum of squares	Mean square	F-value	$F_{.01}$
Total	31	307.6165	-		
Correction of mean	1	98.6124	-		
Patients (ignoring visits and treatments)	16	132.7239	-		
Visits (eliminating patients but ignoring treatments)	1	11.0252	-		
Treatments (eliminating both patients and visits)	3	44.6562	14.8854	7.23	6.55
Remainder	10	20.5988	2.0599		

The differences and 95% comparisonwise confidence intervals for the four treatments means (or effects) are:

	Treatment		
Treatment	C	S	P
I	5.84 ± 2.822*	1.45 ± 2.068	0.94 ± 1.941
P	4.91 ± 3.264*	0.52 ± 2.536	-
S	4.39 ± 2.822*	-	-

* Significant at the 5% level.

Estimated Treatment Effects

	All data	Without 3 discrepant values
$\hat{C}$	3.51	3.78
$\hat{P}$	-0.03	-1.12
$\hat{S}$	-1.26	-0.63
$\hat{I}$	-2.21	-2.06

Treatment I retains bottom position and C retains the top position but the ranks of P and S interchange, depending upon whether the three discrepant values are retained or omitted.

Further study of these data will be made later in the report when the effect of transformation of the data is investigated.

A Statistical Analysis of the Data on Concentration for Visits 4 and 6 with Methacholine

The data for visits 2, 4, and 6 using the mediator methacholine to induce an asthma attack, are presented in Table 10. An analysis of variance table and the estimated effects for treatments and visits 4 and 6 are presented in Table 11. The remainder variance here, 26.3203, is much larger than the variation among patients for visit 2, that is 1.4860. Hence, considerable patient by treatment interaction and/or control by the doctor in visit 2 due to the fact that the study was singly blind and the doctor may not have allowed any patient to take the higher concentrations, must have been present in this experiment. Also, note that the residual mean square 26.3203 for methacholine was 8.5 times larger than the residual mean square 3.0803 using the mediator histamine. As pointed out before the possible range of values was in the ratio of 10/25 = 0.4, and that $(0.4)^2(26.3203) = 4.2$ which is not much different from 3.0803. This result differs from that in Table 6, but there it

Table 10. Concentration at which the methacholine mediator was stopped.

Patient number	Visit (Concentration data) 2	4	6	Total	Sum 4+6	Difference 4-2	Difference 6-2	Sum of 4-2 and 6-2
801	0.31	1.25	25.00	26.56	26.25	0.94	24.69	25.63
802	0.62	0.31	0.31	1.24	0.62	-0.31	-0.31	-0.62
803	0.15	1.25	10.00	11.40	11.25	1.10	9.85	10.95
804	2.50	25.00	25.00	52.50	50.00	22.50	22.50	45.00
805	0.31	0.62	5.00	5.93	5.62	0.31	4.69	5.00
806	0.62	25.00	1.25	26.87	26.25	24.38	0.63	25.01
807	0.15	0.15	5.00	5.30	5.15	0.00	4.85	4.85
808	0.31	0.62	1.25	2.18	1.87	0.31	0.94	1.25
809	1.25	0.62	2.50	4.37	3.12	-0.63	1.25	0.62
810	5.00	25.00	25.00	55.00	50.00	20.00	20.00	40.00
811	0.31	1.25	0.15	1.71	1.40	0.94	-0.16	0.78
812	0.15	0.15	0.62	0.92	0.77	0.00	0.47	0.47
813	0.62	2.50	10.00	13.12	12.50	1.88	9.38	11.26
814	0.62	2.50	5.00	8.12	7.50	1.88	4.38	6.26
815	0.62	0.31	5.00	5.93	5.31	-0.31	4.38	4.07
816	0.31	0.31	1.25	1.87	1.56	0.00	0.94	0.94
817	0.15	1.25	0.62	2.02	1.87	1.10	0.47	1.57
Total	14.00	88.09	122.95	225.04	211.04	74.09	108.95	183.04

Treatment		
$Y_{.P.}$ = 3.72 (8)	$Y_{.P.}$ = 0.63 (8)	
$Y_{.C.}$ = 120.62 (13)	$Y_{.C.}$ = 108.32 (13)	
$Y_{.S.}$ = 79.37 (7)	$Y_{.S.}$ = 69.39 (7)	
$Y_{.I.}$ = 7.33 (6)	$Y_{.I.}$ = 4.70 (6)	

Table 11. Analyses of variance, treatment and visit effects, and treatment covariance matrix for visits 4 and 6 for concentration data in Table 10.

Source of variation	Degrees of freedom	Sum of squares	Mean square	F-ratio	$F_{.05}$
Total	34	4082.0614			
Correction for mean	1	1309.9377			
Patients	16	2102.8571	131.4286		
Visits	1	35.7418	35.7418		
Patient × Visit	16	633.5248	39.5953		
Treatment (eliminating patients × visit)	3	291.3606	97.1202	3.69	3.41
Remainder	13	342.1642	26.3203		
Visit (eliminating treatment)	1	Not computed			

Treatment effects

$\hat{I} = -7.96$
$\hat{S} = 0.52$
$\hat{P} = -2.03$
$\hat{C} = 9.47$

Visit effects

$\hat{v}_4 = 3.89$
$\hat{v}_6 = -3.89$

Covariance matrix/26.3203

$$\begin{bmatrix} .333333 & -.002874 & -.270115 & -.580460 \\ 0 & .284483 & -.258621 & -.534483 \\ 0 & .008621 & .310345 & .241379 \\ 0 & .043103 & .551724 & 1.206897 \end{bmatrix}$$

must be remembered that the doctor may have ruled out high concentrations, thus not allowing the full range of concentrations to be utilized on either visits 1 or 2.

In studying the estimated treatment effects a table of differences between estimated effects as well as the 95% comparisonwise confidence intervals is useful. Such a table is presented below:

Differences between estimated effects (or means) and 95% comparisonwise confidence intervals with methacholine

	Treatment		
Treatment	C	S	P
I	17.43 ± 16.138*	8.48 ± 8.730?	5.93 ± 10.593
P	11.50 ± 9.430*	2.55 ± 10.186	
S	8.95 ± 15.604		

* Significant at the 5% level; ? Almost significant at the 5% level.

From the above we note that treatment C again appears at the top, that is allowing the patient to withstand a higher concentration than the remaining treatments. Treatment C is significantly higher than treatments P and I but not S. Treatment S is significantly higher than treatment I at about the 6% level but not at the 5%. Treatment I appears at the bottom again. It appears to hinder the patients from withstanding as high a concentration level as they would with no treatment, i.e. P. However, this could arise from sampling variation.

The responses to treatments P and I in Table 10 appear to vary relatively little compared to the responses to treatments S and C. This could mean that for asthma attacks induced by the mediator methacholine, considerably different results can be obtained from patient to patient for treatments S and C. This may also be

due to the particular patients who happened to receive these treatments in the 4th and 6th visit. From a study of responses in both Tables 3 and 10, the following five patients appear to respond differently from the remaining 12 patients:

Patient no.	Visit (concentration and treatment) 3	4	5	6	Possible nature
801	0.50 - S	1.25 - I	5.00 - P	25.00 - C	erratic
806	0.12 - I	25.00 - S	10.00 - C	1.25 - P	erratic
810	10.00 - P	25.00 - S	5.00 - I	25.00 - C	uniform-high
814	5.00 - P	2.50 - I	1.00 - S	5.00 - C	erratic
812	0.25 - S	0.15 - I	0.50 - C	0.62 - P	uniform-low

There is a possibility of very uniform responding patients as patient 812, and possibly 806, and of patients with erratic responses. Both these groups contribute to large residuals relative to the remaining patients. An in-depth study of the characteristics of these three groups may throw some light on the nature of this type of response and may indicate differential treatment for the groups. One should also study patient 812, who appears to indicate a slightly increasing concentration ability. Was this psychological? Also, why was patient 810 so tolerant of high concentrations? What caused the erratic behavior of patients 801, 810, and 814?

A Combined Statistical Analysis of the Data on Concentration for Visits 3, 4, 5, and 6

An analysis of variance for the combined data of Tables 3 and 11 is:

Sources of variation	Degrees of freedom		
Total	68		
Correction for the overall mean	1		
Patients	16		
Visits (ignoring treatment effects)	3		
Mediator = Visits 3 + 5 versus 4 + 6		1	
Visits within histamine (3 versus 5)		1	
Visits within methacholine (4 versus 6)		1	
Patients x visits (ignoring treatment effects)	48		
Treatments (eliminating visits; ignoring interactions)		3	
Treatment x mediator (elim. treat., visit and patient)		3	19
Patient x mediator (eliminating all else)		16	
Patient x visit with mediator (elim. treat.)		26	
Within histamine			13
Within methacholine			13

Note that treatments and visits are orthogonal to patients but that patients are not orthogonal to the treatment by mediator interaction effects. These latter effects are estimable, however, as may be noted from the following table of frequency of observations in the 2 x 4 table:

	Treatment				
Mediator	P	I	S	C	Sum
H	9	11	10	4	34
M	8	6	7	13	34
Sum	17	17	17	17	68

A shortened version of the above analysis of variance is presented in Table 12.

Table 12. Analysis of variance, treatment and visit effects, and covariance matrices for concentration data from visits 3, 4, 5, and 6.

Source of variation	Degrees of freedom	Sum of squares	Mean square	F-ratio	$F_{.01}$
Total	68	4539.6779	-	-	
Correction for mean	1	1205.6598	-	-	
Patients	16	1402.3491	87.6468	5.96	2.80
Visits (ignoring treatments)	3	311.7669	-	-	
Treatments (eliminating visits; ignoring interactions)	3	454.9611	151.6537	10.32	4.64
Treatments x mediator plus patient x mediator (eliminating visit, treatment and patient effect)	19	782.7325	41.1964	2.80	2.66
Remainder	26	382.2085	14.7003		
Within histamine	13	40.0443	3.0803		
Within methacholine	13	342.1642	26.3203		

Treatment effects

$\hat{I} = -3.27$
$\hat{S} = 0.99$
$\hat{P} = -2.46$
$\hat{C} = 4.73$

Covariance matrix/14.7003

$$\begin{bmatrix} .068402 & .010294 & -.001184 & -.026902 \\ .009742 & .069730 & -.001696 & -.029373 \\ .000368 & .000408 & .058516 & -.002472 \\ -.017798 & -.019718 & .005079 & .119461 \end{bmatrix}$$

Visit effects

$\hat{V}_3 = -1.05$
$\hat{V}_4 = 1.09$
$\hat{V}_5 = -0.44$
$\hat{V}_6 = 0.40$

Same as above

The treatment x mediator plus the patient x mediator interactions (eliminating treatments, visits, and patient effects) is obtained by subtraction. First the treatment sum of squares for all four visits after eliminating visit effects but ignoring interaction effects is computed. This sum of squares and the residual sum of squares in Tables 4 and 11 are subtracted from the patient x visits (ignoring treatment) sum of squares to produce the interaction sum of squares described above. This interaction sum of squares was not partitioned into its two component parts as it would be necessary to solve 1 + 34 + 8 + 4 normal equations for the various effects to do this. Each of the observations in Table 10 probably should be transformed by multiplying by 0.4 before performing a combined analysis. Also, a logarithmic transformation of the data in both Tables 3 and 10 may be sufficient to equalize residual variances for the two mediators. Despite the need for a transformation, there is little doubt of the significance of the treatment and patient effects or of the interaction. A transformation to achieve stability of variances usually increases the significance of the results.

A study of the visit effects indicates a lack of confounding between treatment C and the fact that the randomization was restricted such that treatment C appeared only in either visit 5 or 6. Since the C effect was so much larger than the remaining effects, the visits 5 plus 6 effect should be larger than the visits 3 plus 4 effect where C did not occur. This was not the case, most likely indicating that the randomization restriction did not confound treatment C with visits 5 and 6 effects.

The treatment design was such that a mixing or interaction effect of treatments can be estimated. First we shall study interactions using an unconventional approach (see page 169 of Federer, loc. cit.) and secondly, a more conventional approach using the analyses for a 2 x 2 factorial. From the treatment effects given in Tables 4, 10, and 12, construct the following tables of zero interaction:

Level of I	Level of S 0	Level of S 1	Histamine Level of S 0	Histamine Level of S 1	Methacholine Level of S 0	Methacholine Level of S 1	H + M Level of S 0	H + M Level of S 1
0	$\hat{P} = x$	$\hat{S} = x + u$	-0.03	-1.26	-2.03	0.52	-2.46	0.99
1	$\hat{I} = x + v$	$\hat{S} + \hat{I} - \hat{P}$	-2.21	-3.44	-7.96	-5.41	-3.27	0.18
Interaction	$\hat{C} - \hat{S} - \hat{I} + \hat{P}$		3.51 + 3.44 = 6.95		9.47 + 5.41 = 14.88		4.73 - 0.18 = 4.55	

Then, the zero interaction may be computed as $(\hat{P} = x) + (\hat{S} - \hat{P} = u) + (\hat{I} - \hat{P} = v) = x + u + v = \hat{S} + \hat{I} - \hat{P}$. Any deviation from this value, either up or down, is interaction. The observed $\hat{C} - (\hat{S} + \hat{I} - \hat{P})$ is a measure of the interaction. This, except for a multiple of 1/2, turns out to be the interaction estimated from a 2 x 2 factorial which is $(\hat{C} - \hat{S} - \hat{I} + \hat{P})/2$.

Now consider a 2 x 2 factorial analysis. Construct the following 2 x 2 tables:

Level of I	Histamine Level of S 0	Histamine Level of S 1	Histamine Sum	Methacholine Level of S 0	Methacholine Level of S 1	Methacholine Sum	H + M Level of S 0	H + M Level of S 1	H + M Sum
0	-0.03	-1.26	-1.29	-2.03	0.52	-1.51	-2.46	0.99	-1.47
1	-2.21	3.51	1.30	-7.96	9.47	1.51	-3.27	4.73	1.46
Sum	-2.24	2.25	0	-9.99	9.99	0	-5.73	5.72	0

Twice the main effects and interactions are:

	H	M	H + M
Main effect of I	2.59	3.02	1.93
Main effect of S	4.49	19.98	11.45
Interaction	6.95	14.88	4.55

Here we see that the effect of treatment I is positive, i.e. the presence of I minus the absence of I produced a positive value, and is a relatively small effect.

The effect of the presence of treatment S over its absence was quite large, as was the positive interaction effect. The variance of 2.59 is obtained as (from Table 4):

$$3.0803[.157407 + .144734 + .168660 + .494019 + .024632 - .046163 + .063884 - 0 - 0 - 0 - .013158 + .092105 + .008373 + .003589 - .180622 - .070574]$$
$$= 2.60866 \ .$$

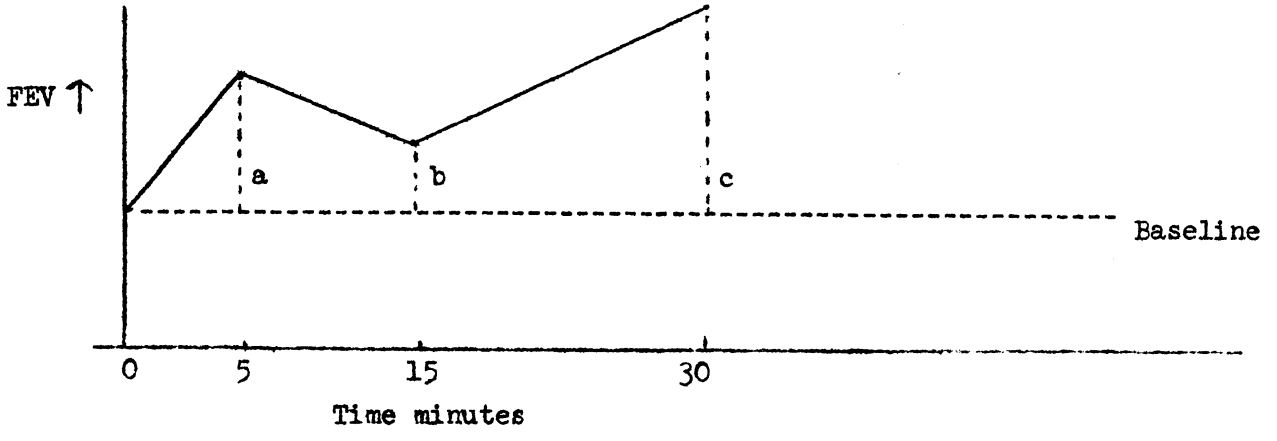
The 95% comparisonwise confidence interval is

$$2.59 \pm 2.160(1.615) = 2.59 \pm 3.49 \ .$$

Thus, the effect of adding treatment I is not significant at the 5% level. The other effects may be handled in a similar manner.

A Statistical Analysis for the Data on Forced Expiratory Volume (FEV) for Visits 3 and 5

Data for forced expiratory volume (FEV) was transformed as follows for FEV data at zero minutes, five minutes, 15 minutes and 30 minutes:



The FEV zero reading is subtracted from each of the five-minute, 15-minute, and 30-minute readings to give values a, b, and c respectively. The area under the above curve is computed as

$$\text{Area} = \frac{5a + 10(a+b) + 15(b+c)}{2} \ .$$

The values a, b, and c may be positive or negative. Thus, the areas can be negative. Since Mr. William Holt found that area values are very variable, it would be best to take square roots of areas. Since some areas are negative, a constant needs to be added to make all values greater than zero. We arbitrarily added 500 to all values and then took square roots to obtain the data in Tables 13 and 14.

Treatment I gave the largest effect with C following. All treatments I, C, and S are larger than the placebo, P, treatment. A more detailed analysis following that in earlier sections could be followed. However, another approach was decided upon. This was because interest centers on the characteristic measurement, for expiratory volume (FEV) in this case, at the initial reading, that is zero minute, and then at five, fifteen, and thirty-minute intervals.

It was decided to study the data from visits 3 and 5 for each treatment P, I, S, and C . The data for FEV for each of the treatments are presented in Tables 15 through 18. A two-way analysis of variance for orthogonal data was performed, a least significant difference = lsd = $t_{.05,\text{error d.f.}} \times \sqrt{\text{variance of a difference between two time means}}$, and the coefficient of variation = (residual mean square)$^{\frac{1}{2}}$ ÷ the overall mean. F-values for patients and times and tabulated F-values are also presented. The patient-to-patient variation for FEV is very large compared to the residual or times mean squares. Likewise, the time-to-time variation is relatively large for treatments S and I and near expectation, 24/22, for treatment P . The latter was to be expected since the P treatments should not affect FEV at any of the time readings. A summary of significance statements for the time means by treatment and using a t-test of significance is presented (see Figure 3).

Table 13. Square root of area plus .500 for forced expiratory volume (FEV).

Patient Number	Visit 3	4	5	6	Total
801	30.822	41.982	11.402	46.341	130.547
802	48.811	48.244	41.443	10.000	148.498
803	42.603	27.568	19.494	33.504	123.169
804	28.592	24.393	32.442	43.590	129.017
805	53.385	25.690	37.483	41.079	157.637
806	48.296	28.638	28.240	17.819	122.993
807	35.143	30.578	47.828	46.824	160.373
808	22.583	48.913	5.244	42.308	119.048
809	32.787	36.912	32.939	34.315	136.953
810	26.833	19.300	28.157	29.453	103.737
811	42.367	26.458	29.707	36.332	134.864
812	14.318	31.345	38.013	15.811	99.487
813	14.748	26.833	5.916	25.397	72.894
814	16.508	31.305	39.655	40.435	127.903
815	29.707	3.536	27.568	40.589	101.400
816	49.219	42.397	47.932	54.863	194.411
817	19.685	42.749	36.469	33.653	132.556
Total	556.407	536.841	509.926	592.313	2195.487

$Y_{.P.} = 366.115$ $Y_{.I.} = 669.737$

$Y_{.S.} = 509.881$ $Y_{.C.} = 649.754$

Table 14. Analysis of variance, treatment and visit effects, and covariance matrices for data in Table 13.

Source of variation	Degrees of freedom	Sum of squares	Mean square	F-ratio	$F_{.01}$
Total	68	80817.5			
Correction for mean	1	70884.7525			
Patients	16	3041.1884			
Visit (ignoring treatment)	3	212.0837			
Patients × visit	48	6679.4754			
Treatments (eliminating visits)	3	2834.6121	944.8707	11.06	4.3
Remainder	45	3844.8633	85.4414		

Treatment effects

$\hat{I} = 7.354$
$\hat{S} = -2.028$
$\hat{P} = -10.854$
$\hat{C} = 5.528$

Covariance matrix/85.4414

$$\begin{bmatrix} .068402 & .010294 & -.001184 & -.026902 \\ .009742 & .069730 & -.001696 & -.029373 \\ .000368 & .000408 & .058516 & -.002472 \\ -.017798 & -.019718 & .005079 & .119461 \end{bmatrix}$$

Visit effects

$\hat{V}_3 = 1.756$
$\hat{V}_4 = -1.497$
$\hat{V}_5 = -1.140$
$\hat{V}_6 = 0.881$

Same as above

Table 15. FEV data for visits 3 and 5 for the P treatment and an analysis of variance of the data.

	Time* (FEV)				
Patient	0	1	2	3	Mean
801	242	233	231	220	231.50
803	330	332	324	322	327.00
804	204	207	221	215	211.75
808	349	344	354	347	348.50
809	237	258	261	254	252.50
810	240	237	251	254	245.50
813	268	246	256	248	254.50
814	242	234	234	233	235.75
817	253	260	268	236	254.25
Mean	262.78	261.22	266.27	258.78	262.36

* 0 = zero minute, 1 = 5 minutes, 2 = 15 minutes, 3 = 30 minutes.

Source of variation	Degrees of freedom	Sum of squares	Mean square	F-ratio	$F_{.05}$
Total - Correction for mean	35	67320.3056	-		
Patient	8	65317.0556	8164.63	114.8	2.36
Time	3	295.6389	98.55	1.39	3.01
Patient x time = residual	24	1707.6111	71.15		

$$\text{lsd} = t_{.05,24}\sqrt{2(71.15)/9} = 8.207$$

Coefficient of variation = 3.2%

Table 16. FEV data for visits 3 and 5 for the I treatment and an analysis of variance of the data.

	Time* (FEV)				
Patient	0	1	2	3	Mean
803	275	320	313	342	312.50
804	221	230	243	249	235.75
805	222	316	308	298	286.00
806	281	348	343	355	331.75
807	293	347	355	374	342.25
809	240	259	256	271	256.50
810	243	254	255	251	250.75
811	391	419	446	444	425.00
815	245	241	261	257	251.00
816	249	307	320	329	301.25
817	231	278	265	238	253.00
Mean	262.82	301.73	305.91	309.82	295.07

* 0 = zero minute, 1 = 5 minutes, 2 = 15 minutes, 3 = 30 minutes.

Source of variation	Degrees of freedom	Sum of squares	Mean square	F-ratio	$F_{.01}$
Total − Correction for mean	43	150008.795	−		
Patient	10	126241.045	12624.1045	46.45	2.98
Time	3	15614.432	5204.8106	19.15	4.51
Residual	30	8153.318	271.7773		

$$\text{lsd} = t_{.05,30}\sqrt{2(271.7773)/11} = 14.354$$

$$\text{msd} = t_{.01,30}\sqrt{2(271.7773)/11} = 19.331$$

Coefficient of variation = 5.6%

Table 17. FEV data for visits 3 and 5 for the S treatment and an analysis of variance of the data.

	Time* (FEV)				
Patient	0	1	2	3	Mean
801	238	246	264	252	250.00
802	267	315	348	335	316.25
805	203	197	249	253	225.50
807	286	331	298	319	308.50
808	365	349	332	373	354.75
812	241	211	233	245	232.50
813	266	251	265	245	256.75
814	237	278	273	279	266.75
815	198	212	213	210	208.25
816	236	325	294	290	286.25
Mean	253.70	271.50	276.90	280.10	270.55

* 0 = zero minute, 1 = 5 minutes, 2 = 15 minutes, 3 = 30 minutes.

Source of variation	Degrees of freedom	Sum of squares	Mean squares	F-ratio	$F_{.05}$
Total - Correction for mean	39	90859.9000	-		
Patient	9	75402.4000	8378.0444	20.03	2.25
Time	3	4163.5000	1387.8333	3.32	2.96
Residual	27	11294.0000	418.2963		

$$\text{lsd} = t_{.05,27}\sqrt{2(418.2963)/10} = 18.769$$

Coefficient of variation = 7.6%

Table 18. FEV data for visits 3 and 5 for the C treatment and an analysis of variance of the data.

	Time* (FEV)				
Patient	0	1	2	3	Mean
802	298	335	342	350	331.25
806	351	375	358	355	359.75
811	441	454	456	454	451.25
812	218	220	254	282	243.50
Mean	327.00	346.00	352.50	360.25	346.44

* 0 = zero minute, 1 = 5 minutes, 2 = 15 minutes, 3 = 30 minutes.

Source of variation	Degrees of freedom	Sum of squares	Mean square	F-ratio	$F_{.05}$
Total - Correction for mean	15	92817.9375	-		
Patient	3	87958.6875	29319.5625	108.28	3.86
Time	3	2422.1875	807.3958	2.98	3.86
Residual	9	2437.0625	270.7847		

$$\text{lsd} = t_{.05,9}\sqrt{2(270.7847)/4} = 26.320$$

Coefficient of variation = 4.7%

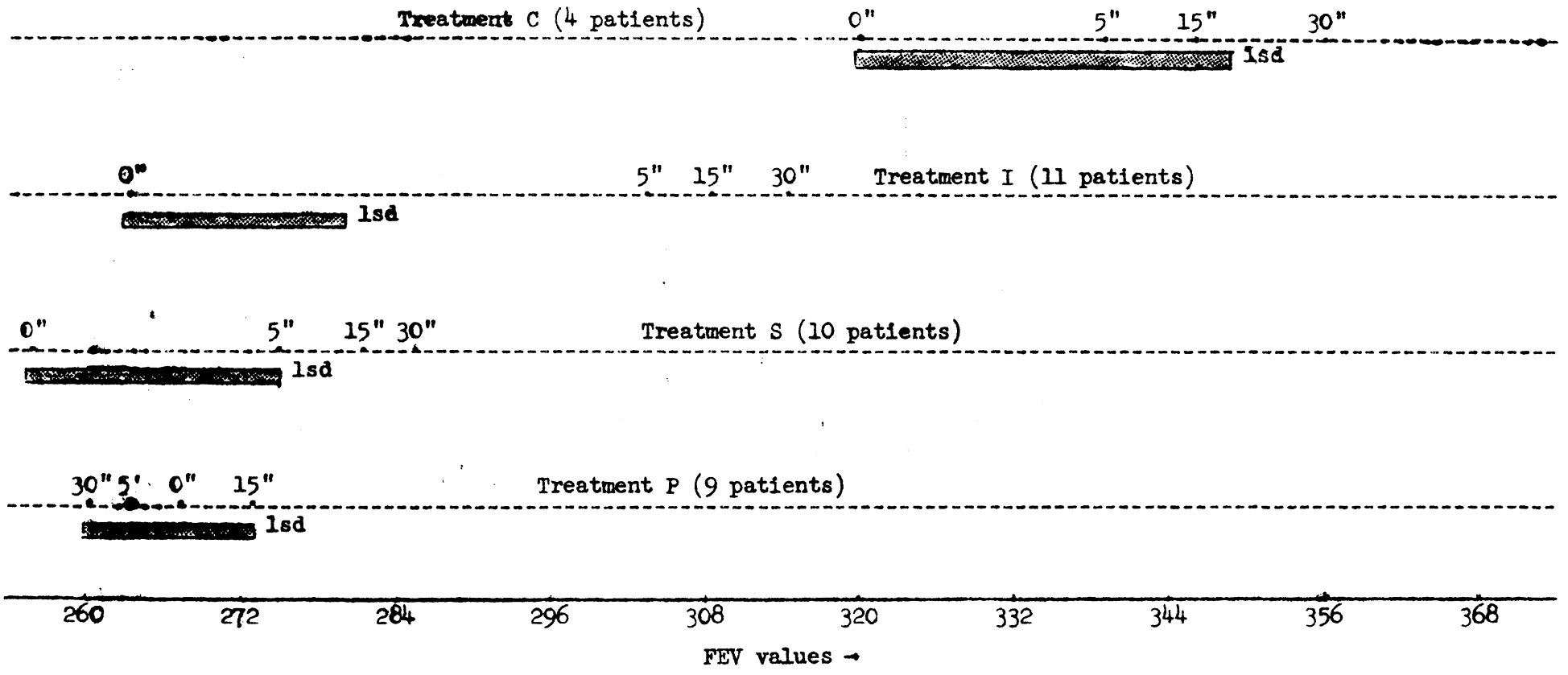


Figure 3. Means of times for FEV measurements on visits 3 and 5 and least significant differences.

P treatment

- No significant differences at the 5% level.

S treatment

- Means for 15" and 30" are significantly higher than the baseline, 0", mean at the 5% level.
- The 5" mean is almost significantly different from the 0" mean at the 5% level.
- Remaining differences of means not significant.

I treatment

- Means for 5", 15", and 30" are significantly higher than the 0" mean at the 1% level.
- Remaining differences between means not significant at the 5% level.

C treatment

- No significant differences among pairs of means at the 5% level although the 15" mean versus the 0" mean is almost significant.

One striking fact about Figure 3 is that the 0-minute reading is so much larger for treatment C than for the remaining three treatments. Of course, only four patients are involved but it would be informative to compare the means of patients 802, 806, 811, and 812 from treatment C with the other treatments as below:

	Patient (patient mean and treatment)				
Visit	802	806	811	812	Mean
3	316.25 - S	331.75 - I	425.00 - I	232.50 - S	326.4
5	331.25 - C	359.75 - C	451.25 - C	243.50 - C	346.4

	Patient (zero(FEV reading and treatment)				
Visit	802	806	811	812	Mean
3	267 - S	281 - I	391 - I	241 - S	295.0
5	298 - C	351 - C	441 - C	218 - C	327.0

The patient means run 20 FEV points higher on visit 5 when treatment C was given than they did on visit 3 when treatments S or I were given. Likewise, for the zero readings only these four patients average 32 FEV points higher on visit 5 than on visit 3. These four patients were about 35 FEV points above the average of all patients receiving treatments P, I, and S. Hence, both sources of variation (sampling?) caused the means to be so far to the right in Figure 3.

A Statistical Analysis for FEV, VC, MMEF, SP, DP, and Pulse Data from Visits 3, 4, 5, and 6.

The six characteristics considered in this section are:

FEV – forced expiratory volume

VC – forced vital capacity

MMEF – (a respiration measurement)

SP – systolic pressure

DP – diastolic pressure

Pulse – heart rate

The data from visits 3 and 5, a table of means, and analyses of variance for these six characteristics are presented in Table 19 for the P treatment, in Table 20 for the I treatment, in Table 21 for the S treatment, and in Table 22 for the C treatment. The analysis of variance tables and means for FEV appear in Tables 15 to 18. The data from visits 4 and 6, a table of means, and analyses of variance for the above six characters appear in Table 23 for treatment P, in Table 24 for treatment I, in Table 25 for treatment S, and in Table 26 for treatment C. The data was subdivided in this manner because the mediator histamine was given on visits 3 and 5 and the mediator methacholine was given on visits 4 and 6.

It was decided by the experimenter that the data from all four visits should be combined. This results in 17 measurements on each of the four times of observation, i.e., 0 = zero minute or baseline, 1 = five minutes, 2 = 15 minutes, and 3 = 30 minutes, for each of the four treatments P, I, S, and C. The pooled means of 17 observations were obtained as a weighted mean of the 3 + 5 and 4 + 6 visits means; that is, data from all 17 patients were used. Instead of rerunning the analyses of variance, the residual sums of squares for visits 3 and 5 and for visits 4 and 6 were combined to obtain a mean square with 45 instead of $48 = (17 - 1)(4 - 1)$ degrees of freedom.

Table 19. Data and analyses for six characteristics for treatment P and visits 3 and 5.

OBS	PAT	VIT	TRT	TIME	FEV	VC	MMEF	SP	DP	PULSE
1	819	3	P	0	253	360	183	110	70	108
2	819	3	P	1	260	363	206	112	68	108
3	819	3	P	2	268	372	218	108	70	108
4	819	3	P	3	236	337	182	130	70	116
5	814	3	P	0	242	302	217	130	84	126
6	814	3	P	1	234	300	203	130	82	122
7	814	3	P	2	234	306	200	130	86	114
8	814	3	P	3	233	302	203	130	82	118
9	813	5	P	0	268	307	315	112	68	94
10	813	5	P	1	246	301	245	100	72	100
11	813	5	P	2	256	291	303	110	70	86
12	813	5	P	3	248	290	283	104	74	86
13	810	3	P	0	240	242	331	108	76	68
14	810	3	P	1	237	239	329	100	62	70
15	810	3	P	2	251	253	373	96	64	70
16	810	3	P	3	254	256	378	92	66	62
17	809	5	P	0	237	239	329	102	80	122
18	809	5	P	1	258	259	456	100	76	114
19	809	5	P	2	261	264	363	98	74	116
20	809	5	P	3	254	256	383	100	74	116
21	808	3	P	0	349	507	247	144	76	94
22	808	3	P	1	344	501	238	140	80	92
23	808	3	P	2	354	511	254	130	70	90
24	808	3	P	3	347	502	245	126	78	88
25	804	3	P	0	204	277	156	118	74	106
26	804	3	P	1	207	273	174	112	70	94
27	804	3	P	2	221	310	150	100	64	92
28	804	3	P	3	215	270	202	108	72	84
29	803	5	P	0	330	429	420	112	62	98
30	803	5	P	1	332	443	454	110	72	100
31	803	5	P	2	324	421	410	118	68	94
32	803	5	P	3	322	429	419	118	62	102
33	801	5	P	0	242	436	111	128	72	116
34	801	5	P	1	233	420	108	124	76	100
35	801	5	P	2	231	439	116	126	74	94
36	801	5	P	3	220	401	105	114	78	100

Table 19 (Continued)

MEANS

TIME	N	VC	MMEF	SP	DP	PULSE
0	9	344.333333	256.555556	118.222222	73.5555556	103.555556
1	9	344.333333	268.111111	114.222222	73.1111111	100.000000
2	9	351.888889	265.222222	112.888889	71.1111111	96.000000
3	9	338.111111	266.666667	113.555556	72.8888889	96.888889
OVERALL MEANS	36	344.666667	264.138889	114.722222	72.6666667	99.111111

ANALYSIS OF VARIANCE FOR VARIABLE VC MEAN 344.666667 C.V. 3.16072176 %

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE
PAT	8	260353.500	32544.1875
TIME	3	858.222	286.0741
RESIDUAL	24	2848.278	118.6782
CORRECTED TOTAL	35	264060.000	7544.5714

ANALYSIS OF VARIANCE FOR VARIABLE MMEF MEAN 264.138889 C.V. 10.0445320 %

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE
PAT	8	357112.556	44639.0694
TIME	3	727.639	242.5463
RESIDUAL	24	16894.111	703.9213
CORRECTED TOTAL	35	374734.306	10706.6944

Table 19 (Continued)

ANALYSIS OF VARIANCE FOR VARIABLE SP		MEAN 114.722222	C.V. 5.46100130 %
SOURCE	DF	SUM OF SQUARES	MEAN SQUARE
PAT	8	5088.22222	636.027778
TIME	3	155.00000	51.666667
RESIDUAL	24	942.00000	39.250000
CORRECTED TOTAL	35	6185.22222	176.720635

ANALYSIS OF VARIANCE FOR VARIABLE DP		MEAN 72.6666667	C.V. 5.23183857 %
SOURCE	DF	SUM OF SQUARES	MEAN SQUARE
PAT	8	966.00000	120.750000
TIME	3	31.11111	10.370370
RESIDUAL	24	346.88889	14.453704
CORRECTED TOTAL	35	1344.00000	38.400000

ANALYSIS OF VARIANCE FOR VARIABLE PULSE		MEAN 99.1111111	C.V. 5.04297424 %
SOURCE	DF	SUM OF SQUARES	MEAN SQUARE
PAT	8	8143.55556	1017.94444
TIME	3	316.44444	105.48148
RESIDUAL	24	599.55556	24.98148
CORRECTED TOTAL	35	9059.55556	258.84444

Table 20. Data and analyses for six characteristics for treatment I and visits 3 and 5.

OBS	PAT	VIT	TRT	TIME	FEV	VC	MMEF	SP	DP	PULSE
1	803	3	I	0	275	391	206	110	78	102
2	803	3	I	1	320	397	337	122	78	94
3	803	3	I	2	313	395	334	120	80	98
4	803	3	I	3	342	428	378	118	78	92
5	804	5	I	0	221	296	138	122	82	104
6	804	5	I	1	230	300	198	118	72	100
7	804	5	I	2	243	317	218	108	70	108
8	804	5	I	3	249	318	235	110	70	92
9	805	3	I	0	222	265	213	114	76	86
10	805	3	I	1	316	372	345	100	62	84
11	805	3	I	2	308	370	327	124	70	88
12	805	3	I	3	298	363	295	116	72	94
13	806	3	I	0	281	301	443	130	90	108
14	806	3	I	1	348	432	363	140	80	112
15	806	3	I	2	343	449	290	140	76	112
16	806	3	I	3	355	464	297	130	70	92
17	807	5	I	0	293	362	288	120	76	106
18	807	5	I	1	347	410	414	126	76	120
19	807	5	I	2	355	419	418	132	70	128
20	807	5	I	3	374	438	469	124	86	128
21	809	3	I	0	240	246	337	100	70	130
22	809	3	I	1	259	260	287	98	68	132
23	809	3	I	2	256	258	383	100	66	128
24	809	3	I	3	271	273	406	100	76	124
25	810	5	I	0	243	256	270	96	60	68
26	810	5	I	1	254	256	408	94	60	72
27	810	5	I	2	255	257	381	96	62	68
28	810	5	I	3	251	253	372	102	72	60
29	811	3	I	0	391	470	381	108	72	94
30	811	3	I	1	419	474	488	110	70	88
31	811	3	I	2	446	487	593	120	74	96
32	811	3	I	3	444	504	547	116	74	88
33	815	5	I	0	245	346	184	112	66	100
34	815	5	I	1	241	325	197	110	62	120
35	815	5	I	2	261	364	202	130	80	130
36	815	5	I	3	257	341	220	112	72	118
37	816	3	I	0	249	268	248	100	66	112
38	816	3	I	1	307	380	264	110	68	110
39	816	3	I	2	320	360	319	98	58	96
40	816	3	I	3	329	415	286	100	66	98
41	819	5	I	0	231	324	183	114	72	104
42	819	5	I	1	278	375	237	128	74	106
43	819	5	I	2	265	358	212	110	72	118
44	819	5	I	3	238	323	203	126	70	100

Table 20 (Continued)

MEANS

TIME	N	VC	MMEF	SP	DP	PULSE
0	11	320.454545	262.818182	111.454545	73.4545455	101.272727
1	11	361.909091	321.636364	114.181818	70.0000000	103.454545
2	11	366.727273	334.272727	116.181818	70.7272727	106.363636
3	11	374.545455	337.090909	114.000000	73.2727273	98.727273
OVERALL MEANS	44	355.909091	313.954545	113.954545	71.8636364	102.454545

ANALYSIS OF VARIANCE FOR VARIABLE VC MEAN 355.909091 C.V. 8.20389468 %

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE
PAT	10	185794.136	18579.4136
TIME	3	19331.091	6443.6970
RESIDUAL	30	25576.409	852.5470
CORRECTED TOTAL	43	230701.636	5365.1543

ANALYSIS OF VARIANCE FOR VARIABLE MMEF MEAN 313.954545 C.V. 15.9161932 %

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE
PAT	10	344394.409	34439.4409
TIME	3	39842.636	13280.8788
RESIDUAL	30	74908.864	2496.9621
CORRECTED TOTAL	43	459145.909	10677.8118

Table 20 (Continued)

ANALYSIS OF VARIANCE FOR VARIABLE SP		MEAN 113.954545	C.V. 5.73452822 %
SOURCE	DF	SUM OF SQUARES	MEAN SQUARE
PAT	10	5054.90909	505.490909
TIME	3	123.90909	41.303030
RESIDUAL	30	1281.09091	42.703030
CORRECTED TOTAL	43	6459.90909	150.230444

ANALYSIS OF VARIANCE FOR VARIABLE DP		MEAN 71.8636364	C.V. 7.47163099 %
SOURCE	DF	SUM OF SQUARES	MEAN SQUARE
PAT	10	1036.18182	103.618182
TIME	3	102.09091	34.030303
RESIDUAL	30	864.90909	28.830303
CORRECTED TOTAL	43	2003.18182	46.585624

ANALYSIS OF VARIANCE FOR VARIABLE PULSE		MEAN 102.454545	C.V. 6.93088129 %
SOURCE	DF	SUM OF SQUARES	MEAN SQUARE
PAT	10	11498.9091	1149.89091
TIME	3	347.2727	115.75758
RESIDUAL	30	1512.7273	50.42424
CORRECTED TOTAL	43	13358.9091	310.67230

Table 21. Data and analyses for six characteristics for treatment S and visits 3 and 5.

OBS	PAT	VIT	TRT	TIME	FEV	VC	MMEF	SP	DP	PULSE
1	816	5	S	0	236	368	161	120	66	92
2	816	5	S	1	325	424	284	110	80	84
3	816	5	S	2	294	358	268	114	70	82
4	816	5	S	3	290	359	258	120	70	74
5	815	3	S	0	198	288	141	130	80	100
6	815	3	S	1	212	305	164	126	78	96
7	815	3	S	2	213	301	162	138	80	108
8	815	3	S	3	210	291	156	140	78	118
9	814	5	S	0	237	320	194	128	80	130
10	814	5	S	1	278	294	288	132	92	110
11	814	5	S	2	273	336	263	124	90	120
12	814	5	S	3	279	346	271	128	88	126
13	813	3	S	0	266	324	275	114	78	104
14	813	3	S	1	251	313	245	100	72	92
15	813	3	S	2	265	312	291	110	70	92
16	813	3	S	3	245	292	248	104	70	88
17	812	3	S	0	241	333	175	120	76	110
18	812	3	S	1	211	311	130	124	74	106
19	812	3	S	2	233	341	164	116	66	106
20	812	3	S	3	245	338	181	122	78	104
21	808	5	S	0	365	524	254	144	84	100
22	808	5	S	1	349	484	240	130	82	112
23	808	5	S	2	332	491	213	140	84	106
24	808	5	S	3	373	536	268	122	80	106
25	807	3	S	0	286	370	254	118	78	102
26	807	3	S	1	331	409	326	116	70	108
27	807	3	S	2	298	406	229	118	72	114
28	807	3	S	3	319	387	326	110	80	110
29	805	5	S	0	203	241	208	112	64	80
30	805	5	S	1	197	240	191	110	68	82
31	805	5	S	2	249	290	254	108	68	76
32	805	5	S	3	253	296	272	108	66	80
33	802	3	S	0	267	487	125	138	72	134
34	802	3	S	1	315	481	189	132	68	114
35	802	3	S	2	348	447	321	114	58	116
36	802	3	S	3	335	498	218	116	66	110
37	801	3	S	0	238	416	120	112	72	118
38	801	3	S	1	246	436	120	120	84	116
39	801	3	S	2	264	457	123	122	78	110
40	801	3	S	3	252	442	122	118	74	102

Table 21 (Continued)

MEANS

TIME	N	VC	MMEF	SP	DP	PULSE
0	10	367.100000	190.700000	123.600000	75.0000000	107.000000
1	10	369.700000	217.700000	120.000000	76.8000000	102.000000
2	10	373.900000	228.800000	120.400000	73.6000000	103.000000
3	10	378.500000	232.000000	118.800000	75.0000000	101.800000
OVERALL MEANS	40	372.300000	217.300000	120.700000	75.1000000	103.450000

ANALYSIS OF VARIANCE FOR VARIABLE VC — MEAN 372.300000 — C.V. 5.90152077 %

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	9	237658.400	26406.4889	
TIME	3	748.000	249.3333	0.52
RESIDUAL	27	13034.000	482.7407	
CORRECTED TOTAL	39	251440.400	6447.1897	

ANALYSIS OF VARIANCE FOR VARIABLE MMEF — MEAN 217.300000 — C.V. 17.8510005 %

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	9	102357.400	11373.0444	
TIME	3	10560.600	3520.2000	2.34
RESIDUAL	27	40626.400	1504.6815	
CORRECTED TOTAL	39	153544.400	3937.0359	

Table 21 (continued)

ANALYSIS OF VARIANCE FOR VARIABLE SP		MEAN 120.700000	C.V. 5.25443181 %
SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	9	3128.40000	347.600000	
TIME	3	126.00000	42.000000	1.04
RESIDUAL	27	1086.00000	40.222222	
CORRECTED TOTAL	39	4340.40000	111.292308	

ANALYSIS OF VARIANCE FOR VARIABLE DP		MEAN 75.1000000	C.V. 5.99009246 %
SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	9	1625.60000	180.622222	
TIME	3	51.60000	17.200000	0.85
RESIDUAL	27	546.40000	20.237037	
CORRECTED TOTAL	39	2223.60000	57.015385	

ANALYSIS OF VARIANCE FOR VARIABLE PULSE		MEAN 103.450000	C.V. 6.76066960 %
SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	9	6974.90000	774.988889	
TIME	3	176.30000	58.766667	1.20
RESIDUAL	27	1320.70000	48.914815	
CORRECTED TOTAL	39	8471.90000	217.228205	

Table 22. Data and analyses for six characteristics for treatment C on visit 5.

OBS	PAT	VIT	TRT	TIME	FEV	VC	MMEF	SP	DP	PULSE
1	802	5	C	0	298	455	171	110	60	122
2	802	5	C	1	335	493	214	130	68	122
3	802	5	C	2	342	499	226	120	76	116
4	802	5	C	3	350	486	248	124	62	128
5	806	5	C	0	351	457	313	136	76	94
6	806	5	C	1	375	499	310	138	70	104
7	806	5	C	2	358	474	285	136	66	98
8	806	5	C	3	355	471	281	130	70	96
9	811	5	C	0	441	504	511	112	66	102
10	811	5	C	1	454	505	574	114	70	112
11	811	5	C	2	456	521	562	110	68	112
12	811	5	C	3	454	512	553	112	72	112
13	812	5	C	0	218	349	200	118	78	98
14	812	5	C	1	220	408	185	120	70	102
15	812	5	C	2	254	344	202	124	74	110
16	812	5	C	3	282	389	204	112	80	102

Table 22 (Continued)

ANALYSIS OF VARIANCE FOR VARIABLE SP MEAN 121.625000 C.V. 4.08579692 %

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value	F.05
PAT	3	1126.75000	375.583333		
TIME	3	108.75000	36.250000	1.47	3.86
RESIDUAL	9	222.25000	24.694444		
CORRECTED TOTAL	15	1457.75000	97.183333		

ANALYSIS OF VARIANCE FOR VARIABLE DP MEAN 70.3750000 C.V. 7.90092472 %

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value	F.05
PAT	3	172.750000	57.5833333		
TIME	3	6.750000	2.2500000	.07	3.86
RESIDUAL	9	278.250000	30.9166667		
CORRECTED TOTAL	15	457.750000	30.5166667		

ANALYSIS OF VARIANCE FOR VARIABLE PULSE MEAN 108.125000 C.V. 4.20727370 %

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-Value	F.05
PAT	3	1292.75000	430.916667		
TIME	3	92.75000	30.916667	1.49	3.86
RESIDUAL	9	186.25000	20.694444		
CORRECTED TOTAL	15	1571.75000	104.783333		

Table 22 (Continued)

MEANS

TIME	N	VC	MMEF	SP	DP	PULSE
0	4	441.250000	298.750000	119.000000	70.0000000	104.000000
1	4	476.250000	320.750000	125.500000	69.5000000	110.000000
2	4	459.500000	318.750000	122.500000	71.0000000	109.000000
3	4	464.500000	321.500000	119.500000	71.0000000	109.500000
OVERALL MEANS	16	460.375000	314.937500	121.625000	70.3750000	108.125000

ANALYSIS OF VARIANCE FOR VARIABLE VC MEAN 460.375000 C.V. 3.69565750 %

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value	F_{05}
PAT	3	43916.2500	14638.7500		
TIME	3	2542.2500	847.4167	2.93	3.86
RESIDUAL	9	2605.2500	289.4722		
CORRECTED TOTAL	15	49063.7500	3270.9167		

ANALYSIS OF VARIANCE FOR VARIABLE MMEF MEAN 314.937500 C.V. 7.50842692 %

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	3	317350.688	105783.563	
TIME	3	1413.688	471.229	0.85
RESIDUAL	9	5032.563	559.174	
CORRECTED TOTAL	15	323796.938	21586.462	

Table 23. Data and analyses for six characteristics for treatment P on visits 4 and 6.

OBS	PAT	VIT	TRT	TIME	FEV	VC	MMEF	SP	DP	PULSE
1	802	6	P	0	244	435	104	112	70	116
2	802	6	P	1	232	359	142	118	66	120
3	802	6	P	2	227	387	106	128	78	120
4	802	6	P	3	231	376	123	102	52	116
5	805	4	P	0	240	294	235	100	70	88
6	805	4	P	1	239	297	237	106	64	90
7	805	4	P	2	239	311	207	108	72	90
8	805	4	P	3	264	348	228	104	74	94
9	806	6	P	0	369	476	315	140	70	86
10	806	6	P	1	367	465	349	134	78	88
11	806	6	P	2	361	480	272	124	70	90
12	806	6	P	3	360	502	229	124	76	92
13	807	4	P	0	308	362	282	114	80	104
14	807	4	P	1	309	399	267	112	78	100
15	807	4	P	2	326	409	305	110	82	98
16	807	4	P	3	335	414	334	112	78	100
17	811	6	P	0	369	469	402	106	68	88
18	811	6	P	1	408	420	421	114	68	88
19	811	6	P	2	401	466	473	116	68	108
20	811	6	P	3	386	455	418	108	74	88
21	812	6	P	0	238	390	146	126	76	102
22	812	6	P	1	215	402	131	140	70	104
23	812	6	P	2	236	398	158	140	80	102
24	812	6	P	3	231	395	135	132	76	106
25	815	4	P	0	237	336	179	138	82	120
26	815	4	P	1	212	292	166	130	80	120
27	815	4	P	2	222	311	172	132	80	124
28	815	4	P	3	222	320	166	130	88	116
29	816	4	P	0	214	280	182	104	60	108
30	816	4	P	1	268	303	270	108	64	96
31	816	4	P	2	250	289	245	106	70	98
32	816	4	P	3	273	332	250	98	64	96

Table 23 (Continued)

MEANS

TIME	N	FEV	VC	MMEF	SP	DP	PULSE
0	8	277.375000	380.250000	230.625000	117.500000	72.0000000	101.500000
1	8	281.250000	367.125000	247.875000	120.250000	71.0000000	100.750000
2	8	282.750000	381.375000	242.250000	120.500000	75.0000000	103.750000
3	8	287.750000	392.750000	235.375000	113.750000	72.7500000	101.000000
OVERALL MEANS	32	282.281250	380.375000	239.031250	118.000000	72.6875000	101.750000

ANALYSIS OF VARIANCE FOR VARIABLE FEV MEAN 282.281250 C.V. 5.15408808 %

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	7	123349.219	17621.3170	
TIME	3	442.094	147.3646	0.70
RESIDUAL	21	4445.156	211.6741	
CORRECTED TOTAL	31	128236.469	4136.6603	

$F_{.10}(3,21) = 2.37$ $F_{.05}(3,21) = 3.07$ $F_{.01}(3,21) = 4.87$

ANALYSIS OF VARIANCE FOR VARIABLE VC MEAN 380.375000 C.V. 5.42168786 %

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	7	124264.500	17752.0714	
TIME	3	2637.750	879.2500	2.07
RESIDUAL	21	8931.250	425.2976	
CORRECTED TOTAL	31	135833.500	4381.7258	

Table 23 (Continued)

ANALYSIS OF VARIANCE FOR VARIABLE MMEF — MEAN 239.031250 — C.V. 12.44

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-Value
PAT	7	282359.219	40337.0313	
TIME	3	1380.844	460.2813	0.52
RESIDUAL	21	18576.906	884.6146	
CORRECTED TOTAL	31	302316.969	9752.1603	

ANALYSIS OF VARIANCE FOR VARIABLE SP — MEAN 118.000000 — C.V. 4.73

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	7	4444.00000	634.857143	
TIME	3	237.00000	79.000000	2.53
RESIDUAL	21	655.00000	31.190476	
CORRECTED TOTAL	31	5336.00000	172.129032	

ANALYSIS OF VARIANCE FOR VARIABLE DP — MEAN 72.6875000 — C.V. 7.20

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	7	1095.87500	156.553571	
TIME	3	69.37500	23.125000	0.84
RESIDUAL	21	575.62500	27.410714	
CORRECTED TOTAL	31	1740.87500	56.157258	

ANALYSIS OF VARIANCE FOR VARIABLE PULSE — MEAN 101.750000 — C.V. 4.654

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-Value
PAT	7	3890.00000	555.714286	
TIME	3	45.00000	15.000000	0.67
RESIDUAL	21	471.00000	22.428571	
CORRECTED TOTAL	31	4406.00000	142.129032	

Table 24. Data and analyses for six characteristics for treatment I on visit 4.

OBS	PAT	VIT	TRT	TIME	FEV	VC	MMEF	SP	DP	PULSE
1	801	4	I	0	205	374	100	112	88	116
2	801	4	I	1	251	414	137	106	78	126
3	801	4	I	2	252	449	112	108	72	104
4	801	4	I	3	249	454	116	108	68	112
5	802	4	I	0	231	411	103	112	66	118
6	802	4	I	1	300	473	168	102	60	112
7	802	4	I	2	304	456	183	112	68	116
8	802	4	I	3	284	413	199	116	76	118
9	808	4	I	0	331	511	204	122	80	96
10	808	4	I	1	379	514	312	124	78	102
11	808	4	I	2	408	544	343	134	74	92
12	808	4	I	3	407	551	316	128	90	94
13	812	4	I	0	245	341	178	110	66	118
14	812	4	I	1	264	361	194	124	70	112
15	812	4	I	2	259	358	188	116	72	116
16	812	4	I	3	267	376	187	112	68	118
17	813	4	I	0	280	312	360	104	60	100
18	813	4	I	1	284	316	342	110	60	106
19	813	4	I	2	288	307	398	104	60	106
20	813	4	I	3	292	310	404	112	62	100
21	814	4	I	0	266	326	264	140	76	134
22	814	4	I	1	291	350	310	120	80	130
23	814	4	I	2	264	346	294	130	84	132
24	814	4	I	3	275	340	265	130	84	126

Table 24 (Continued)

TWO-WAY CLASSIFICATION

MEANS

TIME	N	FEV	VC	MMEF	SP	DP	PULSE
0	6	259.666667	379.166667	201.500000	116.666667	72.6666667	113.666667
1	6	294.833333	404.666667	243.833333	114.333333	71.0000000	114.666667
2	6	295.833333	410.000000	253.000000	117.333333	71.6666667	111.000000
3	6	295.666667	407.333333	247.833333	117.666667	74.6666667	111.333333
OVERALL MEANS	24	286.500000	400.291667	236.541667	116.500000	72.5000000	112.666667

ANALYSIS OF VARIANCE FOR VARIABLE FEV MEAN 286.500000 C.V. 5.646

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	5	48729.0000	9745.80000	
TIME	3	5763.6667	1921.22222	7.34
RESIDUAL	15	3925.3333	261.68889	
CORRECTED TOTAL	23	58418.0000	2539.91304	

ANALYSIS OF VARIANCE FOR VARIABLE VC MEAN 400.291667 C.V. 4.83201853 %

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	5	127911.708	25582.3417	
TIME	3	3655.458	1218.4861	3.26
RESIDUAL	15	5611.792	374.1194	
CORRECTED TOTAL	23	137178.958	5964.3025	

Table 24 (Continued)

ANALYSIS OF VARIANCE FOR VARIABLE MMEF MEAN 236.541667 C.V. 11.76

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-Value
PAT	5	188896.208	37779.2417	
TIME	3	10076.792	3358.9306	4.34
RESIDUAL	15	11610.958	774.0639	
CORRECTED TOTAL	23	210583.958	9155.8243	

ANALYSIS OF VARIANCE FOR VARIABLE SP MEAN 116.500000 C.V. 5.127

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-Value
PAT	5	1898.00000	379.600000	
TIME	3	40.66667	13.555556	0.38
RESIDUAL	15	535.33333	35.688889	
CORRECTED TOTAL	23	2474.00000	107.565217	

ANALYSIS OF VARIANCE FOR VARIABLE DP MEAN 72.5000000 C.V. 8.105

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-Value
PAT	5	1334.00000	266.800000	
TIME	3	46.00000	15.333333	0.44
RESIDUAL	15	518.00000	34.533333	
CORRECTED TOTAL	23	1898.00000	82.521739	

ANALYSIS OF VARIANCE FOR VARIABLE PULSE MEAN 112.666667 C.V. 4.400

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-Value
PAT	5	2859.33333	571.866667	
TIME	3	57.33333	19.111111	0.78
RESIDUAL	15	368.66667	24.577778	
CORRECTED TOTAL	23	3285.33333	142.840580	

Table 25. Data and analyses for six characteristics for treatment S on visit 4.

OBS	PAT	VIT	TRT	TIME	FEV	VC	MMEF	SP	DP	PULSE
1	803	4	S	0	306	418	407	120	66	110
2	803	4	S	1	315	419	428	108	60	108
3	803	4	S	2	316	414	446	100	68	80
4	803	4	S	3	315	419	428	116	64	106
5	804	4	S	0	243	310	223	110	80	84
6	804	4	S	1	232	310	182	112	70	84
7	804	4	S	2	253	319	248	108	70	84
8	804	4	S	3	250	323	226	110	70	76
9	806	4	S	0	366	454	384	130	80	106
10	806	4	S	1	367	475	330	120	76	104
11	806	4	S	2	376	478	345	110	64	96
12	805	4	S	3	391	505	352	118	72	96
13	809	4	S	0	226	228	363	98	70	118
14	809	4	S	1	229	231	341	98	74	100
15	809	4	S	2	274	278	382	94	60	116
16	809	4	S	3	258	261	389	100	60	110
17	810	4	S	0	268	275	295	110	68	74
18	810	4	S	1	264	268	321	92	70	72
19	810	4	S	2	265	267	367	100	66	68
20	810	4	S	3	260	262	387	100	70	66
21	811	4	S	0	332	404	322	90	68	74
22	811	4	S	1	349	432	334	92	64	80
23	811	4	S	2	342	453	283	88	58	78
24	811	4	S	3	325	422	273	92	62	76
25	819	4	S	0	219	341	146	112	70	114
26	819	4	S	1	273	375	220	114	80	108
27	819	4	S	2	270	351	227	108	70	110
28	819	4	S	3	257	349	206	124	78	108

Table 25 (Continued)

MEANS

TIME	N	FEV	VC	MMEF	SP	DP	PULSE
0	7	280.000000	347.142857	305.714286	110.000000	71.7142857	97.1428571
1	7	289.857143	358.571429	308.000000	105.142857	70.5714286	93.7142857
2	7	299.428571	365.714286	328.285714	101.142857	65.1428571	90.2857143
3	7	293.714286	363.000000	323.000000	108.571429	68.0000000	91.1428571
OVERALL	28	290.750000	358.607143	316.250000	106.214286	68.8571429	93.0714286

MEANS

ANALYSIS OF VARIANCE FOR VARIABLE FEV MEAN 290.750000 C.V. 4.4287

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F. value
PAT	6	63563.3333	10593.8883 ~~2880.47619~~	
TIME	3	1403.2500	467.75000	2.99
RESIDUAL	18	2818.6667	156.5926 ~~156.59262~~	
CORRECTED TOTAL	27	67785.2500	2510.56481	

$F_{.10}(3,18) = 2.42$ $F_{.05}(3,18) = 3.16$ $F_{.01}(3,18) = 5.09$

ANALYSIS OF VARIANCE FOR VARIABLE VC MEAN 358.607143 C.V. 3.58585351 %

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	6 ~~7~~	178960.929	29826.8215 ~~25565.8469~~	
TIME	3	1408.679	469.5595	3.01
RESIDUAL	18 ~~17~~	2811.071	156.1706 ~~165.3571~~	
CORRECTED TOTAL	27	183180.679	6784.4696	

Table 25 (Continued)

ANALYSIS OF VARIANCE FOR VARIABLE MMEF MEAN 316.250000 C.V. 9.515

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	6	160635.250	26772.542 ~~22947.8929~~	
TIME	3	2586.393	862.1310	1.01
RESIDUAL	18	15393.607	855.2004 ~~905.5063~~	
CORRECTED TOTAL	27	178615.250	6615.3796	

ANALYSIS OF VARIANCE FOR VARIABLE SP MEAN 106.214286 C.V. 4.837

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	6	2554.71429	425.7857 ~~364.959184~~	
TIME	3	327.28571	109.095238	4.38
RESIDUAL	18	448.71429	24.92857 ~~24.9285758~~	
CORRECTED TOTAL	27	3330.71429	123.359788	

ANALYSIS OF VARIANCE FOR VARIABLE DP MEAN 68.8571429 C.V. 6.749

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	6	496.76190	82.79365 ~~70.96598~~	
TIME	3	179.42857	59.8095238	2.93
RESIDUAL	18	367.23810	20.402117 ~~21.4024709~~	
CORRECTED TOTAL	27	1043.42857	38.6455026	

ANALYSIS OF VARIANCE FOR VARIABLE PULSE MEAN 93.0714286 C.V. 7.2

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	6	6583.85714	1097.3095 ~~940.881020~~	
TIME	3	199.28571	66.428571	1.53
RESIDUAL	18	780.71429	43.373016 ~~45.9246570~~	
CORRECTED TOTAL	27	7563.85714	280.142857	

Table 26. Data and analyses for six characteristics for treatment C on visit 6.

OBS	PAT	VIT	TRT	TIME	FEV	VC	MMEF	SP	DP	PULSE
1	801	6	C	0	206	430	80	114	80	124
2	801	6	C	1	267	452	140	130	76	126
3	801	6	C	2	264	444	134	122	72	128
4	801	6	C	3	268	440	146	120	74	126
5	803	6	C	0	304	392	377	130	66	120
6	803	6	C	1	321	440	473	116	58	106
7	803	6	C	2	337	452	462	110	60	96
8	803	6	C	3	315	439	448	112	70	104
9	804	6	C	0	202	258	176	110	70	80
10	804	6	C	1	251	344	189	118	66	84
11	804	6	C	2	257	330	247	110	70	82
12	804	6	C	3	248	360	136	110	70	88
13	805	6	C	0	228	271	235	98	66	84
14	805	6	C	1	259	324	242	104	70	84
15	805	6	C	2	278	334	282	104	68	82
16	805	6	C	3	272	323	284	106	60	80
17	807	6	C	0	315	386	320	116	80	110
18	807	6	C	1	369	422	476	122	80	110
19	807	6	C	2	379	431	491	120	80	98
20	807	6	C	3	380	441	474	118	80	96
21	808	6	C	0	331	495	223	134	80	90
22	808	6	C	1	365	493	310	130	80	104
23	808	6	C	2	385	506	339	120	72	104
24	808	6	C	3	379	505	328	128	68	100
25	809	6	C	0	244	250	318	100	62	112
26	809	6	C	1	246	248	399	96	70	114
27	809	6	C	2	279	284	423	98	70	110
28	809	6	C	3	274	276	410	100	78	122
29	810	6	C	0	264	277	293	100	62	70
30	810	6	C	1	282	285	365	102	62	68
31	810	6	C	2	276	278	413	100	58	64
32	810	6	C	3	275	278	413	96	54	66
33	813	6	C	0	276	307	331	106	70	86
34	813	6	C	1	274	307	315	108	70	82
35	813	6	C	2	284	303	371	112	72	90
36	813	6	C	3	284	305	396	108	70	92
37	814	6	C	0	242	292	243	138	80	128
38	814	6	C	1	281	347	280	140	78	118
39	814	6	C	2	280	344	278	134	84	116
40	814	6	C	3	291	351	286	136	86	126
41	815	6	C	0	237	325	188	130	72	114
42	815	6	C	1	272	376	213	118	62	120
43	815	6	C	2	285	388	227	124	66	120
44	815	6	C	3	275	359	241	122	64	122
45	816	6	C	0	210	376	128	120	90	88
46	816	6	C	1	306	417	252	118	68	94
47	816	6	C	2	298	406	247	116	74	96
48	816	6	C	3	302	385	287	102	70	96
49	819	6	C	0	277	363	243	122	72	100
50	819	6	C	1	295	379	264	132	84	116
51	819	6	C	2	309	395	275	120	70	124
52	819	6	C	3	290	381	249	120	74	114

Table 26 (Continued)

MEANS

TIME	N	FEV	VC	MMEF	SP	DP	PULSE
0	13	256.615385	340.153846	242.692308	116.769231	73.0769231	100.461538
1	13	291.384615	371.846154	301.384615	118.000000	71.0769231	102.000000
2	13	300.846154	376.538462	322.230769	114.615385	70.4615385	100.769231
3	13	296.384615	372.538462	315.230769	113.692308	70.6153846	102.461538
OVERALL MEANS	52	286.307692	365.269231	295.384615	115.769231	71.3076923	101.423077

ANALYSIS OF VARIANCE FOR VARIABLE FEV MEAN 286.307692 C.V. 4.63542268 %

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	12	73754.0769	6146.17308	
TIME	3	15864.1538	5288.05128	30.02
RESIDUAL	36	6340.8462	176.13462	
CORRECTED TOTAL	51	95959.0769	1881.55053	

$F_{.10}(3,36) = 2.25$ $F_{.05}(3,36) = 2.87$ $F_{.01}(3,36) = 4.40$

ANALYSIS OF VARIANCE FOR VARIABLE VC MEAN 365.269231 C.V. 4.28497381 %

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	12	235792.731	19649.3942	
TIME	3	11100.385	3700.1282	15.10
RESIDUAL	36	8819.115	244.9754	
CORRECTED TOTAL	51	255712.231	5013.9653	

Table 26 (Continued)

ANALYSIS OF VARIANCE FOR VARIABLE MMEF MEAN 295.384615 C.V. 10.03

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	12	456013.808	38001.1506	
TIME	3	51051.846	17017.2821	19.36
RESIDUAL	36	31640.654	878.9071	
CORRECTED TOTAL	51	538706.308	10562.8688	

ANALYSIS OF VARIANCE FOR VARIABLE SP MEAN 115.769231 C.V. 4.258

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	12	6243.23077	520.269231	
TIME	3	151.07692	50.358974	2.07
RESIDUAL	36	874.92308	24.303419	
CORRECTED TOTAL	51	7269.23077	142.533937	

ANALYSIS OF VARIANCE FOR VARIABLE DP MEAN 71.3076923 C.V. 7.13

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	12	2115.07692	176.256410	
TIME	3	56.92308	18.974359	0.73
RESIDUAL	36	931.07692	25.863248	
CORRECTED TOTAL	51	3103.07692	60.844646	

ANALYSIS OF VARIANCE FOR VARIABLE PULSE MEAN 101.423077 C.V. 5.84

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F-value
PAT	12	15231.6923	1269.30769	
TIME	3	35.9231	11.97436	0.34
RESIDUAL	36	1263.0769	35.08547	
CORRECTED TOTAL	51	16530.6923	324.13122	